Hepatitis A

Hepatitis A vaccine is now recommended for routine use in some parts of the country. In fact, we believe the vaccine is beginning to have an impact on the incidence of hepatitis A in some of these areas.

Outbreaks of jaundice -- which were probably hepatitis A -- were reported in the 17th and 18th centuries, often associated with military campaigns. Hepatitis A was originally called infectious hepatitis, and was differentiated epidemiologically from long incubation period hepatitis B in the 1940s. The development of serologic tests in the 1970s helped differentiate hepatitis A from other types of non-B hepatitis. Hepatitis A virus was first isolated in 1979, and a vaccine was first licensed in 1995.

Hepatitis A virus, or HAV, is a picornavirus with an RNA genome. Humans are the only natural host, although several nonhuman primates may be experimentally infected. Depending on conditions, HAV can survive in the environment for months. The virus is relatively stable at low pH levels and moderate temperatures, but can be inactivated by high temperature – above 185^{o} Fahrenheit – formalin, and chlorine. HAV infection is acquired by mouth and the virus replicates in the liver. After 10 to 12 days, virus is present in blood and in the feces. The virus is shed in high titer in the stool of an infected person.

The incubation period of hepatitis A is 15 to 50 days, with an average of about 28 days. Symptomatic illness is not specific for hepatitis A, and is indistinguishable from other types of acute viral hepatitis. Hepatitis A typically has an abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. Clinical illness usually lasts less than 2 months. But 10% to 15% of infected persons have prolonged or relapsing signs and symptoms for up to 6 months. The likelihood of symptomatic illness from HAV infection is directly related to age. Children younger than 6 years of age are usually asymptomatic. Older children and adults usually have symptoms, with jaundice occurring in more than 70% of patients.

Unlike hepatitis B virus, infection with hepatitis A virus does not lead to chronic infection. So complications of hepatitis A are related to the acute disease. 10% to 20% of persons with symptomatic hepatitis A require hospitalization. The overall case fatality rate is about 0.3%, or about one in 330 reported cases. But the fatality rate may be as high as 2% among persons 40 years of age and older. Death is caused by fulminant hepatitis and liver failure. Adults with hepatitis A lose an average of 27 work days per illness. Health departments incur the costs of post exposure prophylaxis for 11 contacts per case. In 1989, the estimated annual cost of hepatitis A in the United States was more than $200 million.

The epidemiology of hepatitis A is beginning to change in the United States. In some populations, it has changed a lot, and we think these changes are because of the vaccine. Hepatitis A is endemic throughout the world. Humans with acute hepatitis A virus infection are the only reservoir. There is no chronic carrier state. Hepatitis A is transmitted by the fecal-oral route, either by direct person to person contact or ingestion of contaminated food or water. The virus is shed in the stool, and is communicable 2 weeks before the onset of illness to about a week after the onset of jaundice.

This graphic shows the source of infection of reported hepatitis A cases in the U.S. from 1990 through 2000. The most frequently reported source of hepatitis A virus infection in the U.S. is sexual or household contact with a person with hepatitis A, accounting for about 14% of reported cases. Men who have sex with men, shown here as MSM, account for about 10%. Daycare attendance or employment, or contact with a child in daycare accounts for about 8% of cases. About 6% of cases had a history of injection drug use, and 5% had a history of recent international travel. About 3% of cases are associated with a suspected food or waterborne outbreak. The source of infection for almost half of persons with hepatitis A is unknown. Groups at increased risk of hepatitis A include international travelers, men who have sex with men, and users of illegal drugs. Outbreaks of hepatitis A have also been reported among persons working with nonhuman primates. This is the only occupational group known to be at increased risk of hepatitis A.

This graph shows reported cases of hepatitis A by year since 1966, when it became nationally reportable as a distinct entity. Reported cases peaked in 1971 with more than 59,000 cases. Notice the cyclic increases in cases about every 10 years. The last peak occurred in 1995. But the incidence of hepatitis A is high even between the peaks. An average of 27,000 cases were reported annually in the United States during the 1990s, with 23,000 cases reported in 1998. It is estimated that for every **reported** case there are 5 to 6 **unreported** cases. That means that more than 100,000 hepatitis A infections occurred in the United States each year during the 1990s. The number of reported cases has fallen since 1998, with about 8,800 cases reported in 2002.

This graph shows the incidence of reported hepatitis A by age group in 1997. The rates are expressed as cases per 100,000 population. The highest incidence of hepatitis A virus infection is among children 5 to 14 years old. This age group accounts for about twenty% of reported cases. Notice that the incidence of reported hepatitis in children younger than 5 years is substantially less than older children. But cases in this age group are grossly under-reported, because most infections in young children are not symptomatic.

One of the most striking features of hepatitis A is its variation by geographic area. The U.S. average annual incidence of hepatitis A during 1987 through 1997 was about 10 cases per 100,000 population. This map shows the average hepatitis A incidence by county during 1987 through 1997. The counties in red had the

highest incidence, 20 or more cases per 100,000 population-that is twice the U.S. average. Counties in orange were next highest, 10 to 19 cases per 100,000. Counties in white had the lowest incidence, zero to 4 cases per 100,000. You can see that the counties shown in red and orange – the counties equal to or higher than the national average – were primarily located in the Pacific northwest, west, southwest, and along the border with Mexico. This map shows hepatitis A incidence in 2001 using the same scale. Notice that the number of high incidence counties has declined remarkably. Some of this decline may be due to the cyclic nature of hepatitis A. But we believe that widespread use of hepatitis A vaccines in high incidence states also contributed.

Many hepatitis A cases in the United States are believed to occur in the context of community wide epidemics. In some communities, epidemics occur every 5 to 10 years and may last for several years. If 65% to 80% first dose vaccination coverage of preschool and school age children is achieved, and routine vaccination of young children is sustained, ongoing outbreaks of hepatitis A can be interrupted. Rates of hepatitis A virus infection fall, and subsequent outbreaks do not occur. Here is an example. This graphic shows the incidence of hepatitis A among American Indians, in the yellow line, and the overall incidence in the U.S., in the blue line. Historically, hepatitis A incidence among American Indians was 6 to 10 times higher than the average U.S. rate. An aggressive hepatitis A vaccination program was begun among American Indian populations soon after the vaccine was licensed in 1995.The decline in incidence, which began in the mid-1990s, has been unprecedented. In 2000, for the first time ever, the rate of hepatitis A among American Indians fell below the average U.S. rate. Hepatitis A has essentially disappeared from communities in which it previously had been endemic and responsible for large community-wide outbreaks.

So, in summary: hepatitis A is a common infection with the highest incidence among children younger than 15 years of age. Although cases occur throughout the U.S., a disproportionate number of cases are reported from just a few states, mostly in the west. The number of cases and rates of disease are falling, in part due to increased use of hepatitis A vaccine in high incidence areas.

Hepatitis A vaccine was first licensed in the United States in 1995. Two hepatitis A vaccines are now available. Both vaccines are inactivated whole virus vaccines. HAVRIX is GlaxoSmithKline's vaccine. VAQTA is made by the Merck Vaccine Division. The vaccines are considered equivalent, and interchangeable. Both are given as a single dose, with a booster dose 6 to 18 months after the first dose. Both vaccines are available in pediatric and adult formulations. Both vaccines are currently approved only for persons 2 years of age and older. The pediatric formulations of both vaccines are for persons 2 through 18 years. The adult formulations are for persons 19 years and older.

Hepatitis A vaccines are highly immunogenic, and large trials have produced estimates of 94% to 100% protection against clinical hepatitis. 95% of adults will develop protective antibody within a month following one dose, and 100% will have protective antibody after two doses. The vaccines are just as impressive in

children 2 and older and in adolescents, with more than 97% seropositive after one dose, and 100% seropositive after two doses. For both vaccines, the booster dose should be based on the person's age at the time of the booster, NOT the age when the first dose was given. For example, if a child received the first dose of the pediatric formulation of VAQTA at 18 years of age, and returns for the booster dose at age 19 years, the booster dose should be the adult formulation, not the pediatric formulation. The minimum interval between the first and booster doses of hepatitis A vaccine is six calendar months. If the interval between the first and booster doses of hepatitis A vaccine is longer than the recommended interval of 6 to 18 months, it's not necessary to repeat the first dose.

Hepatitis A vaccine is also available in a combination vaccine. Twinrix is produced by GlaxoSmithKline, and was licensed by FDA in 2001. It contains a standard adult dose of GSK's hepatitis B vaccine, Engerix, and a pediatric dose of their hepatitis A vaccine, Havrix. The vaccine is administered in a 3 dose series at zero, 1, and 6 to 12 months. Twinrix is approved only for persons 18 years of age and older. No pediatric version of Twinrix is available in the United States. Schedules using combinations of Twinrix and single antigen hepatitis A vaccine have not been studied. We suggest you complete the schedule with the same vaccine that was used for the first dose or doses. If you have your book, please turn to page 184, where there is a discussion of the Twinrix schedule. Contrary to what is in the book at the bottom of page 184, the spacing of Twinrix doses is based on schedule of the hepatitis A component, not the hepatitis B component. The first and second doses should be separated by at least 4 weeks. The second and third doses should be separated by at least FIVE months, not 8 weeks as it says in the book. Please make a note of this error. We thank the alert reader who picked up this mistake.

Since the vaccines were first licensed, the strategy has been to identify and vaccinate two groups of persons: those at high risk for hepatitis A infection and those at high risk for severe sequelae. Targeted vaccination undoubtedly prevented some cases of hepatitis A. But this strategy did not have a significant impact on the burden of disease in the United States. Experience with hepatitis A vaccination in high rate communities shows that routine vaccination of children has had an impact. In 1999, the ACIP voted to move to the next phase of hepatitis A immunization strategy by recommending routine vaccination of children in high incidence areas. These recommendations were published in October, 1999.

ACIP recommends routine hepatitis A vaccination of children 2 years of age and older who live in states, counties, or communities where the average annual hepatitis A rate during 1987 through 1997 was 20 cases per 100,000 population or higher, about twice the national average. The 11 high incidence states are shown on this graphic in green. Only 22% of the U.S. population lived in these states, but half of all hepatitis A cases reported during 1987 through 1997 occurred in them. ACIP also recommends that routine hepatitis A vaccination **should be considered** for children 2 years of age and older who live in states, counties, or communities where the average annual hepatitis A rate during 1987

through 1997 was greater than 10 cases per 100,000 population, but less than 20 per 100,000. States in this category are shown in yellow. These six states accounted for about 12% of the U.S. population, but reported 18% of hepatitis A cases during 1987 through 1997. For the highest incidence states, ACIP recommends routine vaccination throughout the state. The lower incidence states each decide whether to adopt a statewide or a community based vaccination strategy.

ACIP continues to recommend hepatitis A vaccination for groups at increased risk of HAV infection. The traditional high risk groups targeted for hepatitis A vaccination include international travelers, men who have sex with men, drug users, and persons with occupational risk. This group is limited to certain laboratory workers and animal handlers, and does NOT include healthcare workers, or persons with occupational exposure to sewage. Vaccination is also recommended for persons with chronic liver disease including hepatitis C. Persons with chronic liver disease are not necessarily at increased risk of HAV infection, but are at increased risk of complications of hepatitis A. Hepatitis A vaccine should be administered to persons 2 years of age and older traveling to countries with high or intermediate risk of hepatitis A virus infection. These areas include basically the entire world except Canada, Western Europe, Scandinavia, Japan, New Zealand, and Australia. It is assumed that vaccinated persons are protected by 4 weeks after receiving the first dose, although the second dose 6 to 18 months later is still recommended- as a booster.

Available data suggest that 40% to 45% of vaccinated persons may lack neutralizing antibody at 14 days after receiving the first dose. No data are currently available regarding the risk of hepatitis A among persons vaccinated 2 to 4 weeks before departure. Because protection might not be complete until 4 weeks after vaccination, ACIP recommends that persons traveling to a high-risk area less than 4 weeks after the initial dose should also receive immune globulin at a different anatomic injection site. Hepatitis A vaccine is not approved for children less than 2 years of age, so these children should receive immune globulin prior to travel to high-risk areas.

For both hepatitis A vaccines, the most frequently reported adverse reaction following vaccination is a local reaction at the site of injection. Injection site pain, erythema, or swelling is reported in 20% to 50% of recipients. These symptoms are generally mild and self limited. Mild systemic reactions, such as malaise, fatigue, and low grade fever are not common, and are reported in fewer than 10% of recipients. No serious adverse reactions have been reported.

Hepatitis A vaccine should not be administered to persons with a history of a severe allergic reaction to a vaccine component or following a prior dose. Vaccination of persons with moderate or severe acute illnesses should be deferred until the patient has improved. The safety of hepatitis A vaccination during pregnancy has not been determined. However, because it is an inactivated vaccine, the theoretical risk to the fetus is low. The risk associated with vaccination should be weighed against the risk for HAV infection. Because

hepatitis A vaccine is inactivated, no special precautions are needed when vaccinating immunocompromised persons.

Routine hepatitis A vaccination of children is preventing a substantial number of HAV infections. Vaccination of children also eliminates a major source of infection for other children and adults – the group that tends to get more severe disease. Eventually, this strategy will prevent infection in adults who were vaccinated as children, because immunity appears to persist for many years. After nearly a decade of underutilization, hepatitis A vaccine is finally making an impact.

Foodborne outbreaks of hepatitis A do make the news often. ACIP does not recommend **routine** hepatitis A vaccination of food handlers. But the ACIP recommendations give a lot of leeway to state and local public health authorities to institute vaccination of food handlers, based on local circumstances. In fact, we are aware of several counties that have already mandated vaccination of food handlers to try to reduce the risk of food borne outbreaks.